PSJ3

Exhibit 80B

dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence and respiratory depression.

Central Nervous System

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug.

Oxycodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension and to electrical stimulation.

Oxycodone depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Oxycodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of OxyContin® overdose (See **OVERDOSAGE**).

Gastrointestinal Tract And Other Smooth Muscle

Oxycodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System

Oxycodone may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Concentration – Efficacy Relationships

Studies in normal volunteers and patients reveal predictable relationships between oxycodone dosage and plasma oxycodone concentrations, as well as between concentration and certain expected opioid effects, such as pupillary constriction, sedation, overall "drug effect", analgesia and feelings of "relaxation".

As with all opioids, the minimum effective plasma concentration for analgesia will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. As a result, patients must be treated with individualized titration of dosage to the desired effect. The minimum effective analgesic concentration of oxycodone

for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance.

Concentration – Adverse Experience Relationships

OxyContin® Tablets are associated with typical opioid-related adverse experiences. There is a general relationship between increasing oxycodone plasma concentration and increasing frequency of dose-related opioid adverse experiences such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation is altered by the development of tolerance to opioid-related side effects, and the relationship is not clinically relevant.

As with all opioids, the dose must be individualized (see **DOSAGE AND ADMINISTRATION**), because the effective analgesic dose for some patients will be too high to be tolerated by other patients.

PHARMACOKINETICS AND METABOLISM

The activity of OxyContin Tablets is primarily due to the parent drug oxycodone. OxyContin Tablets are designed to provide controlled delivery of oxycodone over 12 hours.

Breaking, chewing or crushing OxyContin Tablets eliminates the controlled delivery mechanism and results in the rapid release and absorption of a potentially fatal dose of oxycodone.

Oxycodone release from OxyContin Tablets is pH independent. Oxycodone is well absorbed from OxyContin Tablets with an oral bioavailability of 60% to 87%. The relative oral bioavailability of OxyContin to immediate-release oral dosage forms is 100%. Upon repeated dosing in normal volunteers in pharmacokinetic studies, steady-state levels were achieved within 24-36 hours. Dose proportionality and/or bioavailability has been established for the 10 mg, 20 mg, 40 mg, 80 mg, and 160 mg tablet strengths for both peak plasma levels (C_{max}) and extent of absorption (AUC). Oxycodone is extensively metabolized and eliminated primarily in the urine as both conjugated and unconjugated metabolites. The apparent elimination half-life of oxycodone following the administration of OxyContin® was 4.5 hours compared to 3.2 hours for immediate-release oxycodone.

Absorption

About 60% to 87% of an oral dose of oxycodone reaches the central compartment in comparison to a parenteral dose. This high oral bioavailability is due to low pre-systemic and/or first-pass metabolism. In normal volunteers, the t½ of absorption is 0.4 hours for immediate-release oral oxycodone. In contrast, OxyContin Tablets exhibit a biphasic absorption pattern with two apparent absorption half-times of 0.6 and 6.9 hours, which describes the initial release of oxycodone from the tablet followed by a prolonged release.

Plasma Oxycodone by Time

Dose proportionality has been established for the 10 mg, 20 mg, 40 mg, and 80 mg tablet strengths for both peak plasma concentrations (C_{max}) and extent of absorption (AUC)

(see Table 1 below). Another study established that the 160 mg tablet is bioequivalent to 2 x 80 mg tablets as well as to 4 x 40 mg for both peak plasma concentrations (C_{max}) and extent of absorption (AUC) (see Table 2 below). Given the short half-life of elimination of oxycodone from OxyContin, steady-state plasma concentrations of oxycodone are achieved within 24-36 hours of initiation of dosing with OxyContin Tablets. In a study comparing 10 mg of OxyContin every 12 hours to 5 mg of immediate-release oxycodone every 6 hours, the two treatments were found to be equivalent for AUC and C_{max}, and similar for C_{min} (trough) concentrations. There was less fluctuation in plasma concentrations for the OxyContin Tablets than for the immediate-release formulation.

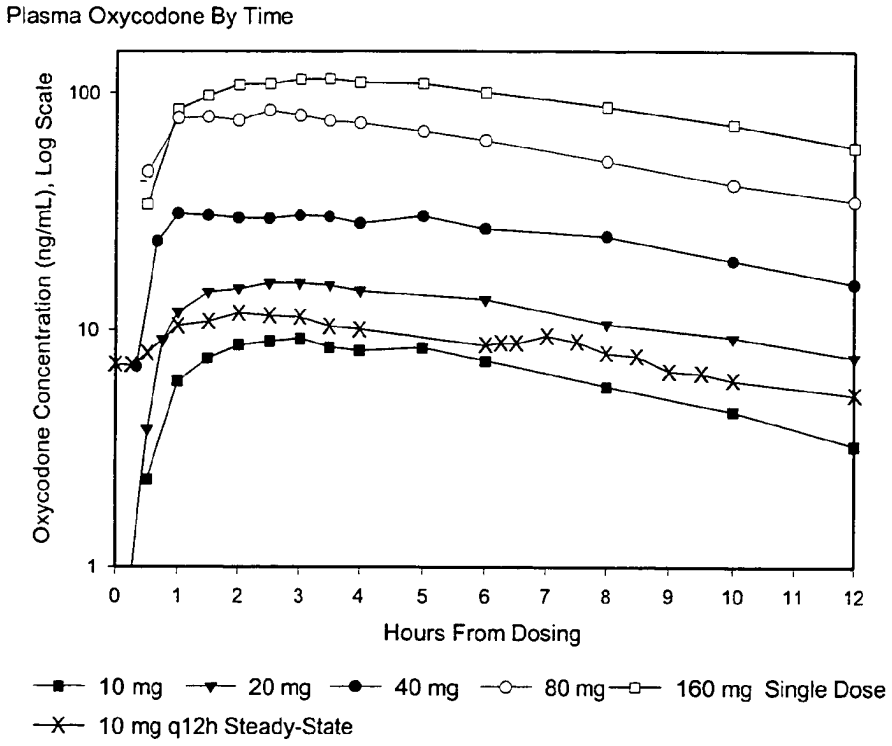

TABLE 1

Mean [% coefficient variation]

Regimen	Dosage Form	AUC (ng•hr/mL)†	C_{max} (ng/mL)	T_{max} (hrs)	Trough Conc. (ng/mL)
Single Dose	10 mg OxyContin	100.7 [26.6]	10.6 [20.1]	2.7 [44.1]	n.a.
	20 mg OxyContin	207.5 [35.9]	21.4 [36.6]	3.2 [57.9]	n.a.
	40 mg OxyContin	423.1 [33.3]	39.3 [34.0]	3.1 [77.4]	n.a.
	80 mg OxyContin*	1085.5 [32.3]	98.5 [32.1]	2.1 [52.3]	n.a.
Multiple Dose	10 mg OxyContin Tablets q12h	103.6 [38.6]	15.1 [31.0]	3.2 [69.5]	7.2 [48.1]
	5 mg immediate-release q6h	99.0 [36.2]	15.5 [28.8]	1.6 [49.7]	7.4 [50.9]

TABLE 2

Mean [% coefficient variation]

Regimen	Dosage Form	AUC_{∞} (ng•hr/mL)†	C_{max} (ng/mL)	T_{max} (hrs)	Trough Conc. (ng/mL)
Single Dose	4 x 40 mg OxyContin*	1935.3 [34.7]	152.0 [28.9]	2.56 [42.3]	n.a.
	2 x 80 mg OxyContin*	1859.3 [30.1]	153.4 [25.1]	2.78 [69.3]	n.a.
	1 x 160 mg OxyContin*	1856.4 [30.5]	156.4 [24.8]	2.54 [36.4]	n.a.

† for single-dose AUC = $AUC_{0\text{-}inf}$; for multiple-dose AUC = $AUC_{0\text{-}T}$

* data obtained while volunteers received naltrexone which can enhance absorption

OxyContin® is NOT INDICATED FOR RECTAL ADMINISTRATION. Data from a study involving 21 normal volunteers show that OxyContin Tablets administered per rectum resulted in an AUC 39% greater and a C_{max} 9% higher than tablets administered by mouth. Therefore, there is an increased risk of adverse events with rectal administration.

Food Effects

Food has no significant effect on the extent of absorption of oxycodone from OxyContin. However, the peak plasma concentration of oxycodone increased by 25% when a OxyContin 160 mg Tablet was administered with a high-fat meal.

Distribution

Following intravenous administration, the volume of distribution (Vss) for oxycodone was 2.6 L/kg. Oxycodone binding to plasma protein at 37°C and a pH of 7.4 was about 45%. Once absorbed, oxycodone is distributed to skeletal muscle, liver, intestinal tract, lungs, spleen, and brain. Oxycodone has been found in breast milk (see **PRECAUTIONS**).

Metabolism

Oxycodone hydrochloride is extensively metabolized to noroxycodone, oxymorphone, and their glucuronides. The major circulating metabolite is noroxycodone with an AUC ratio of 0.6 relative to that of oxycodone. Noroxycodone is reported to be a considerably weaker analgesic than oxycodone. Oxymorphone, although possessing analgesic activity, is present in the plasma only in low concentrations. The correlation between oxymorphone concentrations and opioid effects was much less than that seen with oxycodone plasma concentrations. The analgesic activity profile of other metabolites is not known.

The formation of oxymorphone, but not noroxycodone, is mediated by cytochrome P450 2D6 and, as such, its formation can, in theory, be affected by other drugs (see **Drug-Drug Interactions**).

Excretion

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free oxycodone up to 19%; conjugated oxycodone up to 50%; free oxymorphone 0%; conjugated oxymorphone =14%; both free and conjugated noroxycodone have been found in the urine but not quantified. The total plasma clearance was 0.8 L/min for adults.

Special Populations

Elderly

The plasma concentrations of oxycodone are only nominally affected by age, being 15% greater in elderly as compared to young subjects.

Gender

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. The reason for this difference is unknown.

Renal Impairment

Data from a pharmacokinetic study involving 13 patients with mild to severe renal dysfunction (creatinine clearance <60 mL/min) show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, and AUC values for oxycodone, noroxycodone, and oxymorphone 60%, 50%, and 40% higher than normal subjects, respectively. This is accompanied by an increase in sedation but not by differences in respiratory rate, pupillary constriction, or several other measures of drug effect. There was an increase in t½ of elimination for oxycodone of only 1 hour (see **PRECAUTIONS**).

Hepatic Impairment

Data from a study involving 24 patients with mild to moderate hepatic dysfunction show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, than normal subjects. AUC values are 95% and 65% higher, respectively. Oxymorphone peak plasma concentrations and AUC values are lower by 30% and 40%. These differences are accompanied by increases in some, but not other, drug effects. The t½ elimination for oxycodone increased by 2.3 hours (see **PRECAUTIONS**).

Drug-Drug Interactions (see PRECAUTIONS)

Oxycodone is metabolized in part by cytochrome P450 2D6 to oxymorphone which represents less than 15% of the total administered dose. This route of elimination may be blocked by a variety of drugs (e.g., certain cardiovascular drugs including amiodarone and quinidine as well as polycyclic anti-depressants). However, in a study involving 10 subjects using quinidine, a known inhibitor of cytochrome P450 2D6, the pharmacodynamic effects of oxycodone were unchanged.

Pharmacodynamics

A single-dose, double-blind, placebo- and dose-controlled study was conducted using OxyContin® (10, 20, and 30 mg) in an analgesic pain model involving 182 patients with moderate to severe pain. Twenty and 30 mg of OxyContin were superior in reducing pain compared with placebo, and this difference was statistically significant. The onset of analgesic action with OxyContin occurred within 1 hour in most patients following oral administration.

CLINICAL TRIALS

A double-blind placebo-controlled, fixed-dose, parallel group, two-week study was conducted in 133 patients with chronic, moderate to severe pain, who were judged as having inadequate pain control with their current therapy. In this study, 20 mg OxyContin q12h but not 10 mg OxyContin q12h decreased pain compared with placebo, and this difference was statistically significant.

INDICATIONS AND USAGE

OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

OxyContin is **NOT** intended for use as a prn analgesic.

Physicians should individualize treatment in every case, initiating therapy at the appropriate point along a progression from non-opioid analgesics, such as non-steroidal anti-inflammatory drugs and acetaminophen to opioids in a plan of pain management such as outlined by the World Health Organization, the Agency for Healthcare Research and Quality (formerly known as the Agency for Health Care Policy and Research), the Federation of State Medical Boards Model Guidelines, or the American Pain Society.

OxyContin is not indicated for pain in the immediate postoperative period (the first 12-24 hours following surgery), or if the pain is mild, or not expected to persist for an extended period of time. OxyContin is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society guidelines.)

CONTRAINDICATIONS

OxyContin is contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated. This includes patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment), and patients with acute or severe bronchial asthma or hypercarbia. OxyContin is contraindicated in any patient who has or is suspected of having paralytic ileus.

WARNINGS

OXYCONTIN TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OXYCONTIN TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

OxyContin 80 mg and 160 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

OxyContin® 80 mg and 160 mg Tablets are for use only in opioid-tolerant patients requiring daily oxycodone equivalent dosages of 160 mg or more for the 80 mg tablet and 320 mg or more for the 160 mg tablet. Care should be taken in the prescribing of these tablet strengths. Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death.

Misuse, Abuse and Diversion of Opioids

Oxycodone is an opioid agonist of the morphine-type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

OxyContin has been reported as being abused by crushing, chewing, snorting, or injecting the dissolved product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see **WARNINGS** and **DRUG ABUSE AND ADDICTION**).

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. The development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients.

Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

Interactions with Alcohol and Drugs of Abuse

Oxycodone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

DRUG ABUSE AND ADDICTION

OxyContin® is a mu-agonist opioid with an abuse liability similar to morphine and is a Schedule II controlled substance. Oxycodone, like morphine and other opioids used in analgesia, can be abused and is subject to criminal diversion.

Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common.

"Drug-seeking" behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. OxyContin®, like other opioids, has been diverted for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

OxyContin consists of a dual-polymer matrix, intended for oral use only. Abuse of the crushed tablet poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol and other substances. With parenteral abuse, the tablet

excipients, especially talc, can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Respiratory Depression

Respiratory depression is the chief hazard from oxycodone, the active ingredient in OxyContin®, as with all opioid agonists. Respiratory depression is a particular problem in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Oxycodone should be used with extreme caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of oxycodone may decrease respiratory drive to the point of apnea. In these patients alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

Head Injury

The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in the presence of head injury, intracranial lesions, or other sources of pre-existing increased intracranial pressure. Oxycodone produces effects on pupillary response and consciousness which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

Hypotensive Effect

OxyContin may cause severe hypotension. There is an added risk to individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. Oxycodone may produce orthostatic hypotension in ambulatory patients. Oxycodone, like all opioid analgesics of the morphinetype, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

PRECAUTIONS

General

Opioid analgesics have a narrow therapeutic index in certain patient populations, especially when combined with CNS depressant drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known risks of respiratory depression, altered mental state, and postural hypotension.

Use of OxyContin® is associated with increased potential risks and should be used only with caution in the following conditions: acute alcoholism; adrenocortical insufficiency (e.g., Addison's disease); CNS depression or coma; delirium tremens; debilitated patients; kyphoscoliosis associated with respiratory depression; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; severe impairment of hepatic, pulmonary or renal function; and toxic psychosis.

The administration of oxycodone may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Oxycodone may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings.

Interactions with other CNS Depressants

OxyContin should be used with caution and started in a reduced dosage (1/3 to 1/2 of the usual dosage) in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, other tranquilizers, and alcohol. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with the usual doses of OxyContin.

Interactions with Mixed Agonist/Antagonist Opioid Analgesics

Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as oxycodone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms in these patients.

Ambulatory Surgery and Postoperative Use

OxyContin is not indicated for pre-emptive analgesia (administration pre-operatively for the management of postoperative pain).

OxyContin is not indicated for pain in the immediate postoperative period (the first 12 to 24 hours following surgery) for patients not previously taking the drug, because its safety in this setting has not been established.

OxyContin is not indicated for pain in the postoperative period if the pain is mild or not expected to persist for an extended period of time.

OxyContin is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate (See American Pain Society guidelines).

Patients who are already receiving OxyContin® Tablets as part of ongoing analgesic therapy may be safely continued on the drug if appropriate dosage adjustments are made considering

the procedure, other drugs given, and the temporary changes in physiology caused by the surgical intervention (see **DOSAGE AND ADMINISTRATION**).

OxyContin and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common postoperative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in postoperative patients receiving opioids. Standard supportive therapy should be implemented.

Use in Pancreatic/Biliary Tract Disease

Oxycodone may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids like oxycodone may cause increases in the serum amylase level.

Tolerance and Physical Dependence

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

In general, opioids should not be abruptly discontinued (see **DOSAGE AND ADMINISTRATION: Cessation of Therapy**).

Information for Patients/Caregivers

If clinically advisable, patients receiving OxyContin Tablets or their caregivers should be given the following information by the physician, nurse, pharmacist, or caregiver:

1. Patients should be aware that OxyContin Tablets contain oxycodone, which is a morphine-like substance.

2. Patients should be advised that OxyContin Tablets were designed to work properly only if swallowed whole. OxyContin Tablets will release all their contents at once if broken, chewed, or crushed, resulting in a risk of fatal overdose.

3. Patients should be advised to report episodes of breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.

4. Patients should be advised not to adjust the dose of OxyContin® without consulting the prescribing professional.

5. Patients should be advised that OxyContin may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery).

6. Patients should not combine OxyContin with alcohol or other central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because dangerous additive effects may occur, resulting in serious injury or death.

7. Women of childbearing potential who become, or are planning to become, pregnant should be advised to consult their physician regarding the effects of analgesics and other drug use during pregnancy on themselves and their unborn child.

8. Patients should be advised that OxyContin is a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.

9. Patients should be advised that they may pass empty matrix "ghosts" (tablets) via colostomy or in the stool, and that this is of no concern since the active medication has already been absorbed.

10. Patients should be advised that if they have been receiving treatment with OxyContin for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the OxyContin dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.

11. Patients should be instructed to keep OxyContin in a secure place out of the reach of children. When OxyContin is no longer needed, the unused tablets should be destroyed by flushing down the toilet.

Use in Drug and Alcohol Addiction

OxyContin is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia.

Drug-Drug Interactions

Opioid analgesics, including OxyContin®, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Oxycodone is metabolized in part to oxymorphone via cytochrome P450 2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs including amiodarone and quinidine as well as polycyclic antidepressants), such blockade has not yet

been shown to be of clinical significance with this agent. Clinicians should be aware of this possible interaction, however.

Use with CNS Depressants

OxyContin, like all opioid analgesics, should be started at 1/3 to 1/2 of the usual dosage in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, centrally acting anti-emetics, tranquilizers, and alcohol because respiratory depression, hypotension, and profound sedation or coma may result. No specific interaction between oxycodone and monoamine oxidase inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies of oxycodone to evaluate its carcinogenic potential have not been conducted.

Oxycodone was not mutagenic in the following assays: Ames Salmonella and E. coli test with and without metabolic activation at doses of up to 5000 µg, chromosomal aberration test in human lymphocytes in the absence of metabolic activation at doses of up to 1500 µg/mL and with activation 48 hours after exposure at doses of up to 5000 µg/mL, and in the in vivo bone marrow micronucleus test in mice (at plasma levels of up to 48 µg/mL). Oxycodone was clastogenic in the human lymphocyte chromosomal assay in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1250 µg/mL) at 24 but not 48 hours of exposure and in the mouse lymphoma assay at doses of 50 µg/mL or greater with metabolic activation and at 400 µg/mL or greater without metabolic activation.

Pregnancy

Teratogenic Effects - Category B: Reproduction studies have been performed in rats and rabbits by oral administration at doses up to 8 mg/kg and 125 mg/kg, respectively. These doses are 3 and 46 times a human dose of 160 mg/day, based on mg/kg basis. The results did not reveal evidence of harm to the fetus due to oxycodone. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

OxyContin® is not recommended for use in women during and immediately prior to labor and delivery because oral opioids may cause respiratory depression in the newborn. Neonates whose mothers have been taking oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery.

Nursing Mothers

Low concentrations of oxycodone have been detected in breast milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of an opioid analgesic is

stopped. Ordinarily, nursing should not be undertaken while a patient is receiving OxyContin because of the possibility of sedation and/or respiratory depression in the infant.

Pediatric Use

Safety and effectiveness of OxyContin have not been established in pediatric patients below the age of 18. **It must be remembered that OxyContin Tablets cannot be crushed or divided for administration.**

Geriatric Use

In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone appeared to be slightly reduced. Compared to young adults, the plasma concentrations of oxycodone were increased approximately 15% (see **PHARMACOKINETICS AND METABOLISM**). Of the total number of subjects (445) in clinical studies of OxyContin, 148 (33.3%) were age 65 and older (including those age 75 and older) while 40 (9.0%) were age 75 and older. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected side effects were seen in the elderly patients who received OxyContin. Thus, the usual doses and dosing intervals are appropriate for these patients. As with all opioids, the starting dose should be reduced to 1/3 to 1/2 of the usual dosage in debilitated, non-tolerant patients. Respiratory depression is the chief hazard in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Laboratory Monitoring

Due to the broad range of plasma concentrations seen in clinical populations, the varying degrees of pain, and the development of tolerance, plasma oxycodone measurements are usually not helpful in clinical management. Plasma concentrations of the active drug substance may be of value in selected, unusual or complex cases.

Hepatic Impairment

A study of OxyContin in patients with hepatic impairment indicates greater plasma concentrations than those with normal function. The initiation of therapy at 1/3 to 1/2 the usual doses and careful dose titration is warranted.

Renal Impairment

In patients with renal impairment, as evidenced by decreased creatinine clearance (<60 mL/min), the concentrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal renal function. Dose initiation should follow a conservative approach. Dosages should be adjusted according to the clinical situation.

Gender Differences

In pharmacokinetic studies, opioid-naive females demonstrate up to 25% higher average plasma concentrations and greater frequency of typical opioid adverse events than males, even after adjustment for body weight. The clinical relevance of a difference of this

magnitude is low for a drug intended for chronic usage at individualized dosages, and there was no male/female difference detected for efficacy or adverse events in clinical trials.

ADVERSE REACTIONS

The safety of OxyContin® was evaluated in double-blind clinical trials involving 713 patients with moderate to severe pain of various etiologies. In open-label studies of cancer pain, 187 patients received OxyContin in total daily doses ranging from 20 mg to 640 mg per day. The average total daily dose was approximately 105 mg per day.

Serious adverse reactions which may be associated with OxyContin Tablet therapy in clinical use are those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, and (to an even lesser degree) circulatory depression, hypotension, or shock (see **OVERDOSAGE**).

The non-serious adverse events seen on initiation of therapy with OxyContin are typical opioid side effects. These events are dose-dependent, and their frequency depends upon the dose, the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. They should be expected and managed as a part of opioid analgesia. The most frequent (>5%) include: constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and asthenia.

In many cases the frequency of these events during initiation of therapy may be minimized by careful individualization of starting dosage, slow titration, and the avoidance of large swings in the plasma concentrations of the opioid. Many of these adverse events will cease or decrease in intensity as OxyContin therapy is continued and some degree of tolerance is developed.

Clinical trials comparing OxyContin with immediate-release oxycodone and placebo revealed a similar adverse event profile between OxyContin and immediate-release oxycodone. The most common adverse events (>5%) reported by patients at least once during therapy were:

TABLE 3

	OxyContin (n=227)	**Immediate-Release (n=225)**	**Placebo (n=45)**
	(%)	(%)	(%)
Constipation	(23)	(26)	(7)
Nausea	(23)	(27)	(11)
Somnolence	(23)	(24)	(4)
Dizziness	(13)	(16)	(9)
Pruritus	(13)	(12)	(2)
Vomiting	(12)	(14)	(7)
Headache	(7)	(8)	(7)

Dry Mouth	(6)	(7)	(2)
Asthenia	(6)	(7)	-
Sweating	(5)	(6)	(2)

The following adverse experiences were reported in OxyContin®-treated patients with an incidence between 1% and 5%. In descending order of frequency they were anorexia, nervousness, insomnia, fever, confusion, diarrhea, abdominal pain, dyspepsia, rash, anxiety, euphoria, dyspnea, postural hypotension, chills, twitching, gastritis, abnormal dreams, thought abnormalities, and hiccups.

The following adverse reactions occurred in less than 1% of patients involved in clinical trials or were reported in postmarketing experience.

General: accidental injury, chest pain, facial edema, malaise, neck pain, pain

Cardiovascular: migraine, syncope, vasodilation, ST depression

Digestive: dysphagia, eructation, flatulence, gastrointestinal disorder, increased appetite, nausea and vomiting, stomatitis, ileus

Hemic and Lymphatic: lymphadenopathy

Metabolic and Nutritional: dehydration, edema, hyponatremia, peripheral edema, syndrome of inappropriate antidiuretic hormone secretion, thirst

Nervous: abnormal gait, agitation, amnesia, depersonalization, depression, emotional lability, hallucination, hyperkinesia, hypesthesia, hypotonia, malaise, paresthesia, seizures, speech disorder, stupor, tinnitus, tremor, vertigo, withdrawal syndrome with or without seizures

Respiratory: cough increased, pharyngitis, voice alteration

Skin: dry skin, exfoliative dermatitis, urticaria

Special Senses: abnormal vision, taste perversion

Urogenital: amenorrhea, decreased libido, dysuria, hematuria, impotence, polyuria, urinary retention, urination impaired

OVERDOSAGE

Acute overdosage with oxycodone can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, and death.

Deaths due to overdose have been reported with abuse and misuse of OxyContin®, by ingesting, inhaling, or injecting the crushed tablets. Review of case reports has indicated that the risk of fatal overdose is further increased when OxyContin is abused concurrently with alcohol or other CNS depressants, including other opioids.

In the treatment of oxycodone overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The pure opioid antagonists such as naloxone or nalmefene are specific antidotes against respiratory depression from opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose. In patients who are physically dependent on any opioid agonist including OxyContin, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Please see the prescribing information for the specific opioid antagonist for details of their proper use.

DOSAGE AND ADMINISTRATION

General Principles

OXYCONTIN IS AN OPIOID AGONIST AND A SCHEDULE II CONTROLLED SUBSTANCE WITH AN ABUSE LIABILITY SIMILAR TO MORPHINE. OXYCODONE, LIKE MORPHINE AND OTHER OPIOIDS USED IN ANALGESIA, CAN BE ABUSED AND IS SUBJECT TO CRIMINAL DIVERSION.

OXYCONTIN TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OXYCONTIN TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

One OxyContin 160 mg tablet is comparable to two 80 mg tablets when taken on an empty stomach. With a high-fat meal, however, there is a 25% greater peak plasma concentration following one 160 mg tablet. Dietary caution should be taken when patients are initially titrated to 160 mg tablets (see DOSAGE AND ADMINISTRATION).

In treating pain it is vital to assess the patient regularly and systematically. Therapy should also be regularly reviewed and adjusted based upon the patient's own reports of pain and side effects and the health professional's clinical judgment.

OxyContin® Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-

clock analgesic is needed for an extended period of time. The controlled-release nature of the formulation allows OxyContin to be effectively administered every 12 hours (see **CLINICAL PHARMACOLOGY; PHARMACOKINETICS AND METABOLISM**). While symmetric (same dose AM and PM), around-the-clock, q12h dosing is appropriate for the majority of patients, some patients may benefit from asymmetric (different dose given in AM than in PM) dosing, tailored to their pain pattern. It is usually appropriate to treat a patient with only one opioid for around-the-clock therapy.

Physicians should individualize treatment using a progressive plan of pain management such as outlined by the World Health Organization, the American Pain Society and the Federation of State Medical Boards Model Guidelines. Health care professionals should follow appropriate pain management principles of careful assessment and ongoing monitoring [See **BOXED WARNING**].

Initiation of Therapy

It is critical to initiate the dosing regimen for each patient individually, taking into account the patient's prior opioid and non-opioid analgesic treatment. Attention should be given to:

(1) the general condition and medical status of the patient;
(2) the daily dose, potency, and kind of the analgesic(s) the patient has been taking;
(3) the reliability of the conversion estimate used to calculate the dose of oxycodone;
(4) the patient's opioid exposure and opioid tolerance (if any);
(5) special safety issues associated with conversion to OxyContin® doses at or exceeding 160 mg q12h (see **Special instructions for OxyContin 80 mg and 160 mg Tablets**); and
(6) the balance between pain control and adverse experiences.

Care should be taken to use low initial doses of OxyContin in patients who are not already opioid-tolerant, especially those who are receiving concurrent treatment with muscle relaxants, sedatives, or other CNS active medications (see **PRECAUTIONS: Drug-Drug Interactions**).

For initiation of OxyContin therapy for patients previously taking opioids, the conversion ratios from Foley, KM. [NEJM, 1985; 313:84-95], found below, are a reasonable starting point, although not verified in well-controlled, multiple-dose trials.

Experience indicates a reasonable starting dose of OxyContin for patients who are taking non-opioid analgesics and require continuous around-the-clock therapy for an extended period of time is 10 mg q12h. If a non-opioid analgesic is being provided, it may be continued. OxyContin should be individually titrated to a dose that provides adequate analgesia and minimizes side effects.

1. Using standard conversion ratio estimates (see Table 4 below), multiply the mg/day of the previous opioids by the appropriate multiplication factors to obtain the equivalent total daily dose of oral oxycodone.

2. When converting from oxycodone, divide the 24-hour oxycodone dose in half to obtain the twice a day (q12h) dose of OxyContin.

3. Round down to a dose which is appropriate for the tablet strengths available (10 mg, 20 mg, 40 mg, 80 mg, and 160 mg tablets).

4. Discontinue all other around-the-clock opioid drugs when OxyContin therapy is initiated.

5. No fixed conversion ratio is likely to be satisfactory in all patients, especially patients receiving large opioid doses. The recommended doses shown in Table 4 are only a starting point, and close observation and frequent titration are indicated until patients are stable on the new therapy.

TABLE 4.

Multiplication Factors for Converting the Daily Dose of Prior Opioids to the Daily Dose of Oral Oxycodone*

	(Mg/Day Prior Opioid x Factor = Mg/Day Oral Oxycodone)	
	Oral Prior Opioid	**Parenteral Prior Opioid**
Oxycodone	1	--
Codeine	0.15	--
Hydrocodone	0.9	--
Hydromorphone	4	20
Levorphanol	7.5	15
Meperidine	0.1	0.4
Methadone	1.5	3
Morphine	0.5	3

*** To be used only for conversion to oral oxycodone.** For patients receiving high-dose parenteral opioids, a more conservative conversion is warranted. For example, for high-dose parenteral morphine, use 1.5 instead of 3 as a multiplication factor.

In all cases, supplemental analgesia (see below) should be made available in the form of a suitable short-acting analgesic.

OxyContin® can be safely used concomitantly with usual doses of non-opioid analgesics and analgesic adjuvants, provided care is taken to select a proper initial dose (see **PRECAUTIONS**).

Conversion from Transdermal Fentanyl to OxyContin

Eighteen hours following the removal of the transdermal fentanyl patch, OxyContin treatment can be initiated. Although there has been no systematic assessment of such conversion, a conservative oxycodone dose, approximately 10 mg q12h of OxyContin, should be initially substituted for each 25 µg/hr fentanyl transdermal patch. The patient

should be followed closely for early titration, as there is very limited clinical experience with this conversion.

Managing Expected Opioid Adverse Experiences

Most patients receiving opioids, especially those who are opioid-naive, will experience side effects. Frequently the side effects from OxyContin® are transient, but may require evaluation and management. Adverse events such as constipation should be anticipated and treated aggressively and prophylactically with a stimulant laxative and/or stool softener. Patients do not usually become tolerant to the constipating effects of opioids.

Other opioid-related side effects such as sedation and nausea are usually self-limited and often do not persist beyond the first few days. If nausea persists and is unacceptable to the patient, treatment with antiemetics or other modalites may relieve these symptoms and should be considered.

Patients receiving OxyContin® may pass an intact matrix "ghost" in the stool or via colostomy. These ghosts contain little or no residual oxycodone and are of no clinical consequence.

Individualization of Dosage

Once therapy is initiated, pain relief and other opioid effects should be frequently assessed. Patients should be titrated to adequate effect (generally mild or no pain with the regular use of no more than two doses of supplemental analgesia per 24 hours). Patients who experience breakthrough pain may require dosage adjustment or rescue medication. Because steady-state plasma concentrations are approximated within 24 to 36 hours, dosage adjustment may be carried out every 1 to 2 days. It is most appropriate to increase the q12h dose, not the dosing frequency. There is no clinical information on dosing intervals shorter than q12h. As a guideline, except for the increase from 10 mg to 20 mg q12h, the total daily oxycodone dose usually can be increased by 25% to 50% of the current dose at each increase.

If signs of excessive opioid-related adverse experiences are observed, the next dose may be reduced. If this adjustment leads to inadequate analgesia, a supplemental dose of immediate-release oxycodone may be given. Alternatively, non-opioid analgesic adjuvants may be employed. Dose adjustments should be made to obtain an appropriate balance between pain relief and opioid-related adverse experiences.

If significant adverse events occur before the therapeutic goal of mild or no pain is achieved, the events should be treated aggressively. Once adverse events are under control, upward titration should continue to an acceptable level of pain control.

During periods of changing analgesic requirements, including initial titration, frequent contact is recommended between physician, other members of the healthcare team, the patient and the caregiver/family.

Special Instructions for OxyContin® 80 mg and 160 mg Tablets
(For use in opioid-tolerant patients only.)

OxyContin 80 mg and 160 mg Tablets are for use only in opioid-tolerant patients requiring daily oxycodone equivalent dosages of 160 mg or more for the 80 mg tablet and 320 mg or more for the 160 mg tablet. Care should be taken in the prescribing of these tablet strengths. Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death.

One OxyContin® 160 mg tablet is comparable to two 80 mg tablets when taken on an empty stomach. With a high-fat meal, however, there is a 25% greater peak plasma concentration following one 160 mg tablet. Dietary caution should be taken when patients are initially titrated to 160 mg tablets.

Supplemental Analgesia

Most patients given around-the-clock therapy with controlled-release opioids may need to have immediate-release medication available for exacerbations of pain or to prevent pain that occurs predictably during certain patient activities (incident pain).

Maintenance of Therapy

The intent of the titration period is to establish a patient-specific q12h dose that will maintain adequate analgesia with acceptable side effects for as long as pain relief is necessary. Should pain recur then the dose can be incrementally increased to re-establish pain control. The method of therapy adjustment outlined above should be employed to re-establish pain control.

During chronic therapy, especially for non-cancer pain syndromes, the continued need for around-the-clock opioid therapy should be reassessed periodically (e.g., every 6 to 12 months) as appropriate.

Cessation of Therapy

When the patient no longer requires therapy with OxyContin Tablets, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically dependent patient.

Conversion from OxyContin to Parenteral Opioids

To avoid overdose, conservative dose conversion ratios should be followed.

SAFETY AND HANDLING

OxyContin Tablets are solid dosage forms that contain oxycodone which is a controlled substance. Like morphine, oxycodone is controlled under Schedule II of the Controlled Substances Act.

OxyContin has been targeted for theft and diversion by criminals. Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

HOW SUPPLIED

OxyContin (oxycodone hydrochloride controlled-release) Tablets 10 mg are round, unscored, white-colored, convex tablets bearing the symbol OC on one side and 10 on the other. They are supplied as follows:

NDC 59011-100-10: child-resistant closure, opaque plastic bottles of 100
NDC 59011-100-25: unit dose packaging with 25 individually numbered tablets per card; one card per glue end carton

OxyContin® (oxycodone hydrochloride controlled-release) Tablets 20 mg are round, unscored, pink-colored, convex tablets bearing the symbol OC on one side and 20 on the other. They are supplied as follows:

NDC 59011-103-10: child-resistant closure, opaque plastic bottles of 100
NDC 59011-103-25: unit dose packaging with 25 individually numbered tablets per card; one card per glue end carton

OxyContin (oxycodone hydrochloride controlled-release) Tablets 40 mg are round, unscored, yellow-colored, convex tablets bearing the symbol OC on one side and 40 on the other. They are supplied as follows:

NDC 59011-105-10: child-resistant closure, opaque plastic bottles of 100
NDC 59011-105-25: unit dose packaging with 25 individually numbered tablets per card; one card per glue end carton

OxyContin (oxycodone hydrochloride controlled-release) Tablets 80 mg are round, unscored, green-colored, convex tablets bearing the symbol OC on one side and 80 on the other. They are supplied as follows:

NDC 59011-107-10: child-resistant closure, opaque plastic bottles of 100
NDC 59011-107-25: unit dose packaging with 25 individually numbered tablets per card; one card per glue end carton

OxyContin (oxycodone hydrochloride controlled-release) Tablets 160 mg are caplet-shaped, unscored, blue-colored, convex tablets bearing the symbol OC on one side and 160 on the other. They are supplied as follows:

NDC 59011-109-10: child-resistant closure, opaque plastic bottles of 100
NDC 59011-109-25: unit dose packaging with 25 individually numbered tablets per card; one card per glue end carton

Store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F).

Dispense in tight, light-resistant container.

Healthcare professionals can telephone Purdue Pharma's Medical Services Department

(1-888-726-7535) for information on this product.

CAUTION

DEA Order Form Required.

Purdue Pharma L.P.Stamford, CT 06901-3431

U.S. Patent Numbers 4,861,598; 4,970,075; 5,266,331; 5,508,042; 5,549,912; and 5,656,295

July 18, 2001

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065570-0F-001

PURDUE

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IMPORTANT DRUG WARNING

July 18, 2001

Dear Healthcare Professional,

Reports of illegal misuse, abuse, and diversion of OxyContin® (oxycodone hydrochloride controlled-release) Tablets from various parts of the country have prompted Purdue Pharma L.P. to revise sections of the prescribing information, specifically 1) WARNINGS (including a new Box Warning) which call attention to the potential for misuse, abuse and diversion and 2) INDICATIONS which reinforces the appropriate patient population for whom this product is intended.

OxyContin® is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine. This should be considered when prescribing or dispensing OxyContin® in situations where the prescriber or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. While concerns about abuse, addiction, and diversion should not prevent the proper management of pain, healthcare professionals should be alert to the problems of misuse, abuse, and diversion.

The labeling changes will be implemented within the next several weeks. In the meantime, we want you to be aware of this important safety information. Listed below are highlights of important changes to WARNINGS and INDICATIONS. You should consult the full prescribing information accompanying this letter for all of the changes.

The following BOX WARNING has been added:

WARNING:

OxyContin® is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin® in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

OxyContin® Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

OxyContin® Tablets are NOT intended for use as a prn analgesic.

OxyContin® 80 mg and 160 mg Tablets ARE FOR USE IN OPIOID TOLERANT PATIENTS ONLY. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

OxyContin® (oxycodone hydrochloride controlled-release) TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OxyContin® TABLETS LEADS TO A RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

This is also reinforced in WARNINGS.

The INDICATIONS AND USAGE section now reads:

> OxyContin® Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.
>
> OxyContin® is **NOT** intended for use as a prn analgesic.
>
> Physicians should individualize treatment in every case, initiating therapy at the appropriate point along a progression from non-opioid analgesics, such as nonsteroidal anti-inflammatory drugs and acetaminophen, to opioids in a plan of pain management such as outlined by the World Health Organization, the Agency for Health Research and Quality (formerly known as the Agency for Health Care Policy and Research), the Federation of State Medical Boards Model Guidelines, or the American Pain Society.
>
> OxyContin® is not indicated for pain in the immediate postoperative period (the first 12-24 hours following surgery), or if the pain is mild, or not expected to persist for an extended period of time. OxyContin® is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society guidelines.)

It is important that you forward any adverse event information associated with the use of OxyContin® Tablets to Purdue Pharma L.P. at 1-888-726-7535 (prompt #2). You can also report this information directly to the FDA via the MedWatch system at 1-800-FDA-1088, by fax at 1-800-FDA-0178, by mail (using a postage-paid form), or the Internet at www.FDA.gov/medwatch.

If you have any questions on how to prevent and detect abuse or diversion of this product, you should contact your State Professional Licensing Board or State Controlled Substances Authority for information.

The abuse and diversion of prescription drugs has become a significant public health issue in the United States. Purdue Pharma L.P. is proud to be the first pharmaceutical manufacturer to voluntarily revise prescribing information for a Schedule II opioid in order to address the issue of abuse and diversion.

Sincerely,

Robert F. Reder, MD
Vice President, Medical Affairs and Worldwide Drug Safety

Enclosure

A6846-L-1

Talk Paper

For Internal Use Only – Not For Distribution

U.S. Food and Drug Administration

FDA Talk Paper

FDA Talk Papers are prepared by the Press Office to guide FDA personnel in responding with consistency and accuracy to questions from the public on subjects of current interest. Talk Papers are subject to change as more information becomes available.

T01-30
July 25, 2001

Print Media: 301-827-6242
Broadcast Media: 301-827-3434
Consumer Inquiries: 888-INFO-FDA

FDA STRENGTHENS WARNINGS FOR OXYCONTIN

FDA has strengthened the warnings and precautions sections in the labeling of OxyContin (oxycodone HCl controlled-release) Tablets, a narcotic drug approved for the treatment of moderate to severe pain, because of continuing reports of abuse and diversion.

OxyContin contains oxycodone HCL, an opioid agonist with an addiction potential similar to that of morphine. Opioid agonists are substances that act by attaching to specific proteins called opioid receptors, which are found in the brain, spinal cord, and gastrointestinal tract. When these drugs attach to certain opioid receptors in the brain and spinal cord they can effectively block the transmission of pain messages to the brain. OxyContin is a controlled substance in Schedule II of the Controlled Substances Act (CSA), which is administered by the Drug Enforcement Administration (DEA). Schedule II provides the maximum amount of control possible under the CSA for approved drug products.

In recent months, there have been numerous reports of OxyContin diversion and abuse in several states. Some of these reported cases have been associated with serious consequences including death. In an effort to educate health care providers about these risks, Purdue Pharmaceuticals, manufacturer of the product, has issued a warning in the form of a "Dear Healthcare Professional" letter. The "Dear Healthcare Professional" letter will be distributed widely to physicians, pharmacists, and other healthcare professionals. The letter explains the changes to the labeling including proper prescribing information and highlights the problems associated with the abuse and diversion of OxyContin. OxyContin, like morphine, has a high potential for abuse. It is supplied in a controlled-release dosage form and is intended to provide up to 12 hours of relief from moderate to severe pain. The tablet must be taken whole and only by mouth. When the tablet is crushed and its contents are injected intravenously or snorted into the nostrils, the controlled release mechanism is defeated and a potentially lethal dose of oxycodone is released immediately.

For Internal Use Only – Not For Distribution

FDA has worked with Purdue to make specific changes to the OxyContin labeling. The new labeling is intended to change prescription practices as well as increase the physicians' focus on the potential for abuse, misuse, and diversion.
Changes include a "black box warning", the strongest type of warning for an FDA-approved drug. The new warnings are intended to lessen the chance that OxyContin will be prescribed inappropriately for pain of lesser severity than the approved use or for other disorders or conditions inappropriate for a Schedule II narcotic.

The FDA-approved indication for OxyContin is for the treatment of patients with moderate to severe pain who are expected to need continuous opioids for an extended time. An important factor that must be considered in prescribing OxyContin is the severity of the pain that is being treated, not simply the disease causing the painful symptoms.

FDA continues to recommend that appropriate pain control be provided to patients who are living with severe pain. Although abuse, misuse, and diversion are potential problems for all opioids, including OxyContin, opioids are a very important part of the medical armamentarium for the management of pain when used appropriately under the careful supervision of a physician.

Because of the ongoing problem of OxyContin abuse and diversion, FDA has met with DEA, the Substance Abuse and Mental Health Service Agency, the National Institute on Drug Abuse, Purdue, Inc., and others. FDA will continue to monitor reports of abuse, misuse, and diversion of OxyContin and other opioids and will work with other federal agencies and drug manufacturers to help ensure that these important drugs remain available to appropriate patients.

Since all opioids are subject to abuse, misuse, and diversion, FDA is encouraging all manufacturers of opioids sold in the U.S. to review voluntarily, and revise as necessary, their product's labeling to provide adequate warnings and precautions regarding these risks and to promote responsible prescribing practices.
For more information, patients and healthcare providers can call Purdue Pharmaceuticals at 1-888-726-7535, or go to FDA's website at
www.fda.gov/cder/drug/infopage/oxycontin/.

News Articles

USA Today
August 9, 2001
Page 1A

A reprieve for patients, but a conflict for doctors: Opioids dull unbearable pain and make life livable, but the potential for abuse makes physicians wary

By Rita Rubin

Wife, mother, photographer and community activist Hope Proper disappeared in the late 1980s.

She was replaced by Hope Proper, woman in pain. Nerve damage from an old injury kept her in unremitting agony.

"It becomes your identity," says Proper, 58, of Moorestown, N.J. "You're not you anymore. You are the pain."

Today, Proper has reclaimed some of her former identities and added a few new ones. Like art museum curator.

Like methadone user.

Proper, who has been taking methadone since 1999, considers herself lucky to have found a physician who wasn't afraid to prescribe whatever it took to manage her pain.

Doctors often are reluctant to try opioids -- methadone, morphine and other narcotic painkillers -- for patients who have chronic pain unrelated to cancer. They're afraid that their patients will become hooked, and that they themselves will be slapped with professional sanctions or criminal charges.

Even when physicians are willing to treat chronic pain with opioids, they may hesitate to prescribe enough pills.

"We are deeply suspicious of patients who report pain when they are not bleeding, when they are not dying," says Sandra Johnson, health law and ethics professor at Saint Louis University in Missouri. So millions of adults in the USA are left with inadequately controlled pain that interferes with their ability to sleep, to work, to walk, to enjoy life.

The situation has become more complicated in recent months with reports of widespread abuse of OxyContin, the country's top-selling opioid. OxyContin is a timed-release version of oxycodone, the same opioid as in Percocet and Percodan.

USA Today
(continued)

Swallowed whole as directed, an OxyContin pill gradually releases oxycodone over a 12-hour period. But chewed or crushed and snorted or injected, the pill releases its entire dose of oxycodone at once, giving an immediate high.

That discovery, and some indiscriminate prescribing, has led to a rash of illegal sales, drugstore robberies and reports of homemakers and grandmothers becoming junkies. Pain specialists fear that a resulting backlash might further restrict patients' access to opioids.

An estimated 9% of adults suffer from moderate to severe chronic pain caused by back injuries, arthritis and other non-cancer conditions, according to the American Pain Society. Like Proper, two-thirds of them have lived with pain for more than five years.

"The public health problem represented by misuse of prescription opioids is minuscule in comparison with that of untreated and unrelenting pain," says a statement released by the American Academy of Pain Medicine at its annual meeting this year.

How opioids work

Opioids block transmission of pain messages to the brain by attaching themselves to special proteins in the brain, spinal cord and gastrointestinal tract. Some, like morphine, are derived from opium, while others, like methadone, are synthetic.

In some ways, opioids are safer than other popular painkillers called non-steroidal anti-inflammatory drugs, or NSAIDs, says James Campbell, director of the Blaustein Pain Treatment Program at Johns Hopkins Hospital in Baltimore. NSAIDs such as ibuprofen can damage the liver.

Opioids have no such track record, Campbell says, although they can cause nausea and constipation. But because in the wrong hands they have the potential for abuse, they are controlled substances under the jurisdiction of the U.S. Drug Enforcement Administration.

Proper understands why people might equate opioids with drug abusers. She used to think of them that way herself. Even in the depths of her pain, Proper bridled at the thought of going on opioids. For years, she tried everything but.

"Like everyone else, I assumed I would develop an addiction," Proper says. In her first few years on Dilaudid, her initial opioid, she tried to minimize her chance of becoming addicted by taking a pill only when her pain became unbearable.

Proper says that she now knows better, but that society's misconceptions about opioids continue to dog her. When she applied for long-term-care insurance recently, she was rejected, even though she performed well on memory tests administered by the company.

USA Today
(continued)

"It wasn't the chronicity of the pain that disturbed them," Proper says. "It was the opiates. Because I'm on opioid medications, (the company thought) I'm both cognitively and functionally impaired."

She filed a lengthy appeal, referring to numerous articles in scientific journals. She convinced company officials that she was not living in some methadone-induced fog, and they reversed their earlier decision. "It's one little step for us," Proper says.

Long-term opioid users develop a powerful tolerance for the drugs' sedating effects, Campbell says. They tend to score better on tests of thinking ability because their pain is under control.

When a specialist first suggested opioids for pain resulting from abdominal surgeries in 1993, images of strung-out junkies came to Diane Keybida's mind. She thought she would never be able to return to work as a dental hygienist. It took several sessions with a psychologist before she could accept the thought of taking the drugs.

"I realized if I'm going to have any life, I have to take these pills," says Keybida, 47, of Califon, N.J.

Before she went on opioids, Keybida says, she could barely walk, let alone bale hay and repair heavy machinery, as she used to on her family's small farm. She planned her life so that she would have to descend the stairs of her two-story home only once a day.

For the past four years, Keybida has been taking sustained-release morphine pills three times a day. If necessary, she'll take a "rescue dose" whenever the pain gets too severe. She still isn't up to seeing as many patients at her husband's dental practice as she did before the pain hit. And she hasn't resumed her strenuous farm chores.

"It's still good days, bad days," she says. Although the pain is still there, "it's not bringing me to tears."

Even doctors who want to specialize in treating pain share patients' and society's misconceptions about opioids, says Russell Portenoy, Keybida's and Proper's doctor. When doctors enter Portenoy's training program at Beth Israel Medical Center in New York, where he chairs the department of pain medicine and palliative care, "it's a huge eye-opener."

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From 30 to 200 tablets

The first shock, he says, is the size of a prescription. For pain expected to last only a few weeks or so, doctors are used to writing a non-refillable prescription for, say, 30 tablets. For patients with chronic pain, who measure their suffering in years, he's likely to write a prescription for 200 tablets. Patients sometimes develop a tolerance for opioids' pain-killing effects and require larger doses.

Joseph Saccomanno of Patterson, N.Y., has had firsthand experience with physicians' fears about opioids. After Saccomanno suffered a herniated disc while lifting computer monitors nine years ago, one doctor never prescribed quite enough medication to control

his searing back pain. So he started taking five OxyContin pills a day instead of the prescribed four. That fifth dose, he says, enabled him to go to the mall with his kids.

Suspected of being a junkie

When Saccomanno, 44, ran out of pills several days early and sought more, his doctor suspected him of being a junkie and ordered him into detox. Saccomanno says that while most of his fellow detox patients were taking methadone to break their addictions to illicit drugs, he was discovering how much the drug helped relieve his back pain.

Doctors as well as patients confuse addiction with physical dependence, Portenoy says. Like most people who take an opioid regularly for a few days or more, Saccomanno is physically dependent on methadone. If he were to stop taking it, he would experience withdrawal.

But it's not the withdrawal depicted in movies, with victims bouncing off walls in distress, Portenoy says. "It looks like the flu," he says. "In some people, very mild, in some people, not so mild."

Addiction, with its powerful psychological component, is different. "You're exhibiting drug-seeking behavior, and you're acting irrationally," says Terry Woodworth, deputy director of the DEA's diversion control office.

To help enlighten doctors, the Federation of State Medical Boards three years ago adopted model guidelines for the use of controlled substances in treating pain.

The guidelines recommend that doctors complete a thorough medical history and physical examination before drawing up a written treatment plan. In addition, doctors should periodically review the treatment course, paying special attention to patients who are at risk for misusing their medications, such as those with a history of substance abuse or a psychiatric disorder along with pain.

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Dale Austin, the group's interim chief executive director, says 48 of 69 member boards have adopted the guidelines. "If physicians are embracing those guidelines in their practice, that will keep them out of trouble from a regulatory standpoint," Austin says.

But it's too early to tell whether the guidelines have led to improved treatment of chronic pain, says Johnson of Saint Louis University. "The boards are mentally committed to use these guidelines," she says. "I'm hopeful, but right now it is just on paper."

Doctors who have been trained in treating pain say they can recognize the signs of opioid abuse and nip it before it escalates.

"I think of one patient out of maybe 300 or 400 patients where we were pretty suspicious that there was an abuse issue," Campbell says. "There was a pattern of lost prescriptions. Inconsistent stories. Claiming to be very disabled, but you call up, and the patient's never at home."

Portenoy says he won't even necessarily stop prescribing opioids to a patient who is abusing them. There are ways to control addictive behaviors, he says, such as writing prescriptions for small amounts of pills and doing drug screens on patients' urine samples.

In all his years of treating pain, Portenoy says, he has had to take only a few patients off opioids because of abuse. "But you know, I'm very prepared for that."

Los Angeles Times
August 13, 2001
Health; Part S; Page 1

OxyContin Abuse May Curb Progress in Pain Field

Riddled with pain from rheumatoid arthritis and a degenerative bone disease for years, Diana Rose rarely left the house. Then in November, a doctor prescribed the painkiller **OxyContin,** dramatically changing her quality of life.

By Linda Marsa, Times Health Writer

"I can actually go shopping at the mall, play with my grandchildren and even swim in our pool," said Rose, a 57-year-old Kentucky woman. "This drug has enabled me to do things without being in pain."

OxyContin, a powerful drug that is a chemical cousin to opiates such as morphine and heroin, has enabled thousands of people, such as Rose, to resume the normal activities of life. But now some doctors fear that a backlash triggered by rampant street use of the drug dubbed "hillbilly heroin" will derail significant advances in the field of pain management. They worry that U.S. drug officials may respond to rising illicit use of OxyContin by yanking it from the market, place stricter limits on the use of all opiates, commonly used to treat cancer patients, severe back pain and other chronic pain conditions.

"This is not just about OxyContin," said John D. Giglio, executive director of the American Pain Foundation, a nonprofit consumer group in Baltimore. "This is about the potential for rolling back progress made in pain management. It's been an extremely hard uphill climb to get physicians to become more comfortable prescribing opiates and overcoming the stigma among patients about potential addiction and abuse."

OxyContin is a synthetic opiate that has fewer side effects than other potent pain medications, including morphine or codeine, which can cause nausea, constipation or drowsiness. What's more, OxyContin is formulated to keep steady levels of the drug circulating in the blood for as long as 12 hours. Patients don't experience the intense peaks and valleys of taking other narcotics, like Vicodin or Lortab, which can take an hour to provide pain relief and whose effects wear off in four hours.

Soon after OxyContin was approved in 1995, recreational drug users discovered that chewing the pill, rather than letting it dissolve in the gastrointestinal tract, crushing it into a power that can be snorted or intravenously injected, produced an intense high. Within a few years, Appalachian communities in Virginia, West Virginia and Kentucky, and rural Maine reported a wave of users who had become addicted to the drug.

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Since then, illicit use of the drug has spread throughout the country. It is estimated that more than 200,000 Americans have abused the drug, which also has been implicated in more than 100 deaths from suspected overdoses. Several doctors have been convicted of illegally dispensing the drug, while "Oxy" addicts increasingly turn to crime to feed their habits.

The growing alarm about illicit use is having a chilling effect on legitimate use of the drug. Six states--Florida, Maine, Ohio, South Carolina, Vermont and West Virginia--have set strict limits on the number of pills that can be prescribed for people on Medicaid, the state-federal health program for the poor. That means that doctors may not be able to increase dosages for patients who need stronger pain relief.

In the wake of several robberies at drugstores across the country, many pharmacies now refuse to stock it, and physicians are reluctant to prescribe it.

"Since all this hysteria began, some patients have been abandoned by their doctors," said Dr. J.S. Hochman, executive director of the National Foundation for Treatment of Pain in Houston. "I had two patients, a mother and daughter with severe rheumatoid arthritis who had to fly from Boston to Houston to find a doctor--and were willing to do so because they were so desperate. It's pathetic."

Some patients are so concerned about the negative publicity, especially fears of addiction, that they've asked their doctors to take them off the drug.

"The day after an OxyContin story aired on one of the TV newsmagazines, I had two cancer patients come in the next day, telling me they wanted off the drug," said Dr. Neal Slatkin, director of supportive and palliative medicine at City of Hope National Medical Center in Duarte.

"Their pain was well-controlled, and they weren't having side effects," he said. "So I spent a lot of time reassuring them that this drug was OK. But the whole incident was very distressing."

Patients who continue taking the drug often face serious obstacles in getting their prescriptions. In Pulaski, Va., for example, a small town in Appalachia, police began fingerprinting patients who had OxyContin prescriptions. Under threat of a lawsuit by the American Civil Liberties Union, authorities later backed down.

"I've been refused treatment in the ER because they think I'm a drug seeker," said Jeannette Murray. The 31-year-old nurse, who lives in an area of southwestern Virginia that is a hotbed of OxyContin addiction, takes the drug to relieve chronic pain from an injury to her right arm.

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"It's been difficult finding a pharmacy to get my prescription filled," Murray said. "I've been cautioned not to carry my prescription on my person, which just adds more stress to an already stressful situation."

In response to reports of OxyContin abuse, Purdue Pharma, a Stamford, Conn., pharmaceutical firm, in May stopped marketing the 160-mg version of the drug, then the strongest dosage available.

The company also recently announced plans to introduce a "smart" version of the pills, which lose their potency if they're crushed or snorted; however, the new formulation won't be available for a few years.

And beginning in July, the FDA required that OxyContin boxes carry the agency's strongest warning: a black box label that calls attention to the drug's potential for abuse and diversion.

"But all this hoopla just exacerbates patients' underlying anxiety about taking opiates, which we know are really quite effective," said Dr. Richard Payne, chief of pain and palliative care service at Memorial Sloan-Kettering Cancer Center in New York.

"There is still a pervasive undertreatment of pain," he said, "and thousands of people are suffering needlessly."

GRAPHIC: PHOTO: OxyContin, nicknamed 'hillbilly heroin,' is a synthetic opiate.
PHOTOGRAPHER: LAWRENCE K. HO/Los Angeles Times

Pittsburgh Post-Gazette
August 6, 2001
Pg.A-5

A Low Dose Works for Him

Randy Klugh says OxyContin has helped him become his old self again.

In 1997, the West Deer resident suffered a severe whiplash injury when the Chevy pickup he was driving was hit from behind at a stoplight. The older-model Chevy didn't have a headrest, and Klugh's head smashed straight back into the glass window.

Doctors performed surgery to repair several neck discs, but he continued to have painful muscle spasms and excruciating headaches.

The sole breadwinner for his family, Klugh, 37, tried to work through the pain, but his taxing job as a heavy equipment mechanic aggravated his condition.

After he was referred to The Western Pennsylvania Hospital's pain clinic, Dr. Jack Kabazie performed several nerve blocks to deaden some of the pain, but Klugh still needed medication. He tried several drugs, such as high doses of Motrin or the narcotic analgesic Vicodin, but they were "ripping my stomach apart," because he had to take so many pills.

"Some made him into a zombie," said his wife, Sharon. "When you have a job to do or have three children, you can't be a zombie. You may be out of pain, but what good are you?"

Klugh once was in so much pain he nearly fainted when his oldest daughter gave him a big bear hug. There were times he could not hold his infant daughter and he had to quit coaching girl's softball.

Kabazie put him on 20 milligrams of OxyContin, a relatively low dose.

"Taking these meds, I turned into a normal dad," he said. "Without them, I stayed in my room and paced back and forth. He's [Kabazie] put me back on the planet."

His wife agreed. "It made him able to function at work, function as a father and not be all drugged up. Not to be in Never-Never Land."

He has taken a new job within his company that is not as strenuous and has been able to resume coaching softball.

Klugh said he feels bad about the abuse of OxyContin. "It aggravates me because finally I find something that works for me, and it just happens to be the 'in' drug."

The Orange County Register
August 5, 2001
SECTION: Commentary

A drug war-- The government has turned its attention to the pain-killer OxyContin. Is the scare campaign justified?

By Alan W. Bock

Ralph Murray of Mission Viejo was a meat cutter for 15 years before carpal tunnel syndrome, several surgeries and a host of wrist and hand ailments pushed him onto disability. Despite surgeries (perhaps in part because of them; they uncovered deeper neural problems than his surgeons suspected) he has severe chronic pain -- it hurts all the time.

"OxyContin is the only medication I've found that lets me sleep pain-free all night," he told me recently. With other prescription pain medications I had to get up and take a pill every four hours. If I didn't set an alarm the pain would wake me soon enough, and then it would take a while for the medication to kick in. I know it is potentially addictive and I discussed all the ramifications with my doctor thoroughly before starting it. But it's really been a blessing."

Murray had tried several prescription pain medications before trying OxyContin. Neurontin didn't touch his particular pain, even in progressively heavier doses. Vicodin, which combines the opioid hydrocodone with acetaminophen, helped some.

However, as Eric Chevlen, an assistant professor of medicine at Northeastern Ohio Universities College of Medicine wrote in a recent Weekly Standard article, acetaminophen in large doses (Murray was taking 12 a day) carries a risk of serious liver damage.

So Murray has paid close attention to the spate of scare stories about OxyContin in recent weeks.

The Food and Drug Administration has announced that it will henceforth carry the agency's strongest warning, a black box calling it potentially addictive as morphine. The Drug Enforcement Agency has announced a high-profile campaign to nail doctors and pharmacists it deems responsible for abuse. The little town of Pulaski in southwest Virginia wants to require pharmacists who dispense OxyContin to require patients to provide fingerprints.

Doctors in Philadelphia and Florida have been arrested for over-prescribing OxyContin. An ambitious lawyer has filed a suit against the drug's manufacturer, Purdue Pharma of Stamford, Conn., for getting people hooked.

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Of course, most of the media, ever cooperative whenever the drug warriors identify a new Drug Menace of the Month and provide a couple of anecdotal horror stories, have been only too happy to feed the panic. National Public Radio, feeding off a Washington Post story, did an alarmed take on OxyContin in Virginia last week. Time, Newsweek, The New York Times and the Philadelphia Inquirer have all done tales of abuse and diversion replete with lurid details.

As happened during the crack cocaine epidemic of the 1980s, the media stories raising alarms and tut-tutting about this latest favorite of junkies have informed millions of people who would otherwise never have heard of Oxy- Contin that there's a new drug out there, and informed them how to abuse it. Thousands of people who would otherwise not have learned of OxyContin will try it.

Some will become addicted or die, the self-fulfilling prophecy will play itself out, and thousands of people will be hooked as a result of publicity that those who pushed it claimed was supposed to be helpful.

Surely the drug warriors have to be intelligent enough to know that this is the dynamic.

Why is OxyContin so useful to those in chronic pain and why is it subject to abuse?

As Eric Chevlen explained, OxyContin's active ingredient, oxycodone, an opioid (apparently the preferred term these days for what used to be generally called narcotics), has been in pharmaceutical use in the United States for 60 years. (Dr. Standiford Helm, Ralph Murray's doctor, a principal at the Pacific Coast Medical Center in Newport Beach, which specializes in pain management, says the ingredient has been separated and used medicinally since the Middle Ages.)

What Purdue Pharma did was figure out a way to put it in a time-release formula, so the drug is released gradually over 12 hours, maintaining a steady presence in the bloodstream.

What those who want to use OxyContin as a recreational or escapist euphoric do is crush the tablets, nullifying the time-release qualities, and have a tablet with large doses of straight oxycodone, which is apparently similar to heroin in characteristics, and quite addictive. Having subverted the qualities that make OxyContin so useful to people in chronic pain, they snort or inject this substance.

In the last several years a good deal of attention has been paid to the problem of treating intractable pain in the United States. Heroin was first effectively outlawed, as Dr. Helm reminded me not by an outright ban, but by declaring that chronic pain was not a specific disease, and treating it with potentially addictive opium derivatives like heroin was therefore outside the scope of medical practice.

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Medical authorities now recognize chronic pain -- sometimes clearly attributable to a specific injury or illness, less often with unknown origins -- as a condition in and of itself.

Patients and eventually Congress have held hearings on the inadequacy of treatment of intractable pain, and Congress passed a law mandating federal authorities to study ways to eliminate barriers to adequate pain treatment.

Chevlen estimates that 30 million to 50 million Americans live in chronic pain. Dr. Helm would put the figure at 20 million to 30 million. Both figures are huge, and most authorities estimate that only about a quarter of them are getting adequate treatment, even with advances in understanding in the last few years.

OxyContin has become quite widely used since its approval by the Food and Drug Administration in December 1995, growing from almost zero to about 6 million prescriptions in 2000.

With its increased popularity has come some diversion from legitimate medical uses to the recreational or persistent junkie market. It seems to be a fairly serious problem in some rural Appalachian areas, where serious pain is fairly widespread due to mining and agricultural injuries and the authorities have little experience dealing with black market drug problems.

The question is, to what extent is diversion and abuse a problem and what kinds of actions might minimize such problems.

Chevlen points out that last year about 16,000 Americans died from treating arthritis with drugs like Advil and Aleve, because these medications increase the risk of bleeding ulcers and liver problems when used over long periods. About 200 people died in the same time period from purposeful abuse -- using in ways it was clearly not intended to be used -- of OxyContin. Naturally, the government in its wisdom has decided the 200 deaths constitute the problem that requires a public campaign and new restrictions.

In a letter responding to Chevlen's article Laura Nagel, the DEA deputy assistant administrator, used the numbers that have appeared in most news stories, but in a fascinating way. The number of OxyContin prescriptions has increased 20-fold since 1996, she said, and the number of oxycodone-related incidents -- emergency room and medical examiner reports -- have increased by 400 percent and 100 percent respectively.

But that's comparing apples to rocks. A 20-fold increase in prescriptions is a 2,000 percent increase. You could say, with some justification, that increases in reports of abuse that are 1/20 to 1/8 the increase in total prescriptions suggests that diversion into the black market so far is a relatively minor problem -- far from inconsequential and certainly tragic for those who have become addicted or have died, but not worthy of a full-court-press publicity campaign.

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The DEA has suggested two control programs. The first is cutting back on overall production of OxyContin -- DEA administrator Donnie Marshall suggested rolling back quotas to 1996 levels, which would be a 95 percent cutback from current levels. The second is allowing only pain management specialists to prescribe OxyContin.

There is no universally accepted criterion or licensing standard for pain management specialization, but Chevlen estimates there are about 3,000 pain management specialists in the country, concentrated in urban areas. If the total number of people in chronic pain is only 20 to 30 million, that's a heck of a caseload for those practitioners -- or, more likely, millions of Americans deprived of effective relief.

Why would the DEA propose such a cruel remedy to a problem whose magnitude is dubious and which it has purposely hyped and pumped up? It's a familiar and fundamental dynamic, in my view. It might help to consider the institutional incentives facing an agency like the DEA. Every bureaucracy, private or public, has an incentive to grow and increase its authority, power, influence and prestige. If the government ever really won" the War on Drugs the DEA and related agencies would face the possibility of going out of business.

Their incentive, then, is to magnify perception of the problems they are facing to convince journalists to help them sell the perception of a crisis and Congress to increase their funding. This has worked well over the years. Journalists are notoriously mathematically illiterate and have their own vested interest in perceived crises. Politicians love to respond to perceived crises with more programs and more of the taxpayers' money.

Politicians and journalists are subsets of the general population populated by greater percentages of people whose instinctive response to a perceived problem is to propose a new government program or more government spending as the obvious, logical and inevitable response. In the case of hard drugs, however, there's a compelling case that this approach is dead wrong.

The black markets for drugs, which increase profit margins for sellers to obscene levels and are marked by crime and violence, are created by heavy-handed government controls. The more draconian the controls, the more lucrative the illicit trade.

In addition, controls feed into the American culture's (and maybe humankind's) eternal propensity to avoid personal responsibility. Few people want to acknowledge the role played by their own bad choices in creating their personal problems. The stance of the victim -- of a troubled childhood, a bad neighborhood, lack of opportunity, racism, corporate greed, or an all-powerful drug that makes one helpless -- is more psychologically attractive to many and is encouraged by the general culture.

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But any addiction specialist, while acknowledging that these and other factors are important, will tell you that the addict taking personal responsibility for his or her own choices is important, perhaps essential to recovery. The world is full of conditions that impact people deleteriously over which they have no control. The key, as the Serenity Prayer puts it, is to accept the things you cannot change so you can begin to change the things you cannot accept.

Piling on the controls designed to save people from themselves deters and delays the acceptance of personal responsibility. You can make a case that it prolongs drug abuse problems rather than resolving or fixing them.

Besides the Weekly Standard magazine, these questions have also been raised mainly by drug-reform groups like the Lindesmith Center and DRCNet.

OxyContin provides invaluable relief to a wide variety of people who suffer from chronic pain. It is also subject to misuse and abuse. It is tempting to want to use government to try to control those problems. But much of the evidence suggests that will only make the problem worse. The public spinning of worst-case scenarios may have done so already.